Addition or Amendment to the Drawings:

The application as originally filed did not include any drawings. Attached to this amendment is a proposed drawing Figure 1 which is a generalized schematic illustrating the different materials which result in different areas of a phase diagram. These materials, or phases, are well understood by those of skill in the art and are discussed in detail in the application beginning at the bottom of page 7 of the application and extending up to the top of page 29 of the application.

At the interview, the Examiner requested entry of the attached drawing to provide diagram which will assist in understanding the different phase materials. Consideration and approval of the entry of the attached Figure 1 in the next office action is requested. A formal drawing will be prepared and provided on allowance of the claims.

REMARKS

The Applicant and the undersigned thank the Examiner for the interview which took place on November 22, 2005. This amendment makes the discussions which took place at the interview of record in the case.

At the interview, basic differences between emulsions and both L3 and liquid crystalline phase materials were discussed in detail. The application discusses L3 phase materials on page 14, at lines 12 et seq., microemulsions and emulsions at page 16 at line 16 et seq. and page 19, at line 12 et seq., and liquid crystalline phase materials on page 20, at line 20 et seq. A variety of other materials of different phases, see discussion in the application on pages 7-29, were discussed during the interview, and the drawing Figure 1 was discussed at the interview. At the interview it was agreed that the generalized drawing provided a good graphical depiction of different phases in the context of a phase diagram, and showed the different phase materials set forth within the patent application specification. In response to the Examiner's request at the interview, Figure 1 is being added to the application and the specification is being amended to recognize a Figure 1 as part of the application. No new matter is presented.

Claims 1, 27, 44, 52, and 53 have been amended, and claims 61-64 have been added. The application now includes claims 1, 3-27, and 29-64. Similar to claim 57 which is limited to a liquid crystalline phase material for the structured fluid, claims 61-64 require that the structured fluid be a liquid crystalline phase that is either cubic or reverse hexagonal. New claims 61-64 fall within the ambit of the elected species and are properly considered at this time. As will be demonstrated below, independent claims 1 and 27 are allowable over the prior art of record. In view of this, dependent claims 20-26 and 45-51, which were previously withdrawn, should be rejoined and allowed with the next office action.

Claims 1, 3-19, 27, 29-44, 52, 53, and 56-60 have been rejected as being obvious over a combination of Lambert in view of Bener and Azuma. This rejection is traversed in view of the amendments above and comments below.

The crux of the invention set forth in the specification is the use of an essential oil to bring an otherwise insoluble compound (the active) with it into a

structured fluid, that is, into the liquid crystal or other structured fluid phase. The active is thus solubilized in the liquid crystal phase by use of and with the essential oil. The specification contains an extended discussion as to the advantages of having certain active drugs solubilized in liquid crystalline phases, including enhanced absorption, enhanced stability, targeting potential, etc. The independent claims highlight this aspect of the invention by requiring that the compound is present in an effective amount in said structured fluid.

As the Examiner will recognize, the emulsion of Lambert is not a structured fluid, that is selected from the group of liquid crystalline phase and L3 phase materials. Further, the Lambert does not teach or suggest a liquid crystalline phase or L3 phase material in which the compound is present in an effective amount. Both requirements are set forth in the independent claims of the application. Rather, as noted in column 6, line 50, Lambert contemplates the tocopherol to be present in the oil phase. In sharp contrast, the claimed invention contemplates the compound that is difficult to solubilize being in the structured fluid (which is either liquid crystalline phase or L3 phase) in an effective amount. Emulsions, of course, are not cubic liquid crystalline phase, reversed hexagonal liquid crystalline phase, or even L3 phase materials, and do not have the attributes of holding the compound tightly within the structure of the structured fluid so as to allow slow release and/or to provide protection from degrading agents.

For purposes of this response U.S. Patent 6,458,373 to Lambert and US Patent Publication 2003/0104015 to Lambert will be treated as one and the same reference since U.S. Patent Publication 2003/0104015 is a continuation of U.S. Patent 6,458,373. Lambert describes using an emulsion to deliver taxol, with taxol being present in the oil phase (which is neither an L3 phase nor a liquid crystalline phase). This can be seen by referencing claim 1 of U.S. Patent 6,458,373 to Lambert where it is stated that "wherein all of the chemotherapeutic agent is in the oil phase" and claim 1 of U.S. Patent Publication 2003/0104015 to Lambert where it is stated "wherein said composition is in the form of an emulsion or a micellar solution". With reference to column 6, lines 50-54 and column 15, lines 53-55 of Lambert is stated that the therapeutic is soluble in the "oil phase" and that the thereapeutic paclitaxel remains solubilized "only in the

presence of the α-tocopherol domain", respectively. Nowhere in Lambert is there any teaching or suggestion of having a drug present in an effective amount in an L3 or liquid crystalline phase (e.g., Lambert does not teach that the difficultly solubilized drug becomes solubilized in an L3 or liquid crystalline phase).

As will be recognized by those skilled in the art, emulsions of hydrophobic drugs contain the drug in large volumes of oil phase, which are surrounded by and stabilized by a surfactant mono- or multi-layer. The function of the surfactant mono- or multi-layer is to stabilize the oil phase (oil droplets) in which the drug is contained, not to solubilize drug. This is what is taught in Lambert.

The Examiner has relied on Benet for its teaching of spearmint oil, purportedly for increasing the bioavailibility of pharmaceuticals. The Examiner will recognize that Benet has no teaching whatsoever concerning solubilizing a pharmaceutical or other bioactive in effective amounts within an L3 or liquid crystalline phase structural fluid. The addition of spearmint oil (as per Benet) to the emulsion of Lambert will not produce a structured fluid with drug and oil solubilized and present in the structured fluid, but simply a different kind of emulsion containing more oil in which the drug continues to be present in the (now more voluminous) oil phase. At different ratios and mixing routines, such a course may under certain circumstances produce at best a gamisch of emulsion and small volumes of other phases, but there will not be an effective amount of the drug solubilized in the liquid crystalline phase(s). This can be readily seen with reference to basic principles of emulsions and structured fluids; and in turn this can be most readily understood by use of a phase diagram, the basic tool in this area.

The Examiner has relied upon Azuma for its teaching of gentisic acid which is used commonly as an antioxidant. The Examiner will recognize that Azuma has no teaching whatsoever concerning solubilizing a pharmaceutical or other bioactive in effective amounts within an L3 or liquid crystalline phase structural fluid. The sole mention in Azuma of "gentisic acid" is at Col 4, Line 15 – 19, where it is stated: "in addition to said essential components, the non-radioactive [diagnostic] carrier may include any conventional additives such as an antioxidant (e.g. . gentisic acid) or a preservative." Of course, the

antioxidant property of gentisic acid is well recognized (see the present application at page 39, line 25), as well as the lack of claims in Azuma for this property. In Azuma, there is no discussion about the addition of gentisic acid serving any function other than for antioxidation properties. Gentisic acid is not identified by Azuma as having any effect on the carrier itself, either physically or in its function or properties. At the levels used, it could not affect phase behavior or increase solubilization. One skilled in the art will recognize that adding gentisic acid, in any amount, to the Lambert plus Benet formulation above, will not create a structured fluid that is a lyotropic liquid crystal where drug is solubilized therein..

At best, the combination of Lambert, Benet and Azuma would result in an emulsion (note Benet is also directed to an emulsion) which includes drug and/or other agents in the oil phase. The combination would not make obvious to one of ordinary skill in the art having an effective amount of the compound in the structured fluid selected from L3 phase or liquid crystalline phase material as is required in the independent claims 1, 27, 52, and 53, and would not make obvious having the drug in a cubic liquid crystalline or reverse hexagonal phase as is required in claims 61-64.

As discussed at the interview, in the area of lipid based systems, different mixtures of the same ingredients do not produce the same physical materials. As well recognized phase diagrams show (new Figure 1 being representative of information which can be obtained from a variety of sources), the same ingredients when mixed in different proportions can yield vastly different nanostructures with vastly different implications for solubilizing pharmaceutical agents. Lambert, by his own repeated teachings in his patent, worked to locate the active pharmaceutical solely in the pure oil phase of emulsions, which oil phase is not even a nanostructured material. Benet and Azume do not even address the problem of solubilization of actives, nor even recognize the existence of nanostructured fluids. Nor is there any reason to believe any nanostructured fluid is present in their work.

In the art as known to a skilled artisan as practiced, the phases (in particular, structured fluids) are plotted on a phase diagram, revealing the equilibrium phases at each possible combination of the components. The precise

rules, as well as the mathematics governing the phase equilibria described by the phase diagram, were the master work of Josiah Williard Gibbs in the last century, a work considered to be of the highest importance in the field of chemistry (see, On the Equilibrium of Heterogeneous Substances, Eds. James D. & ES Dana, and B. Silliman), Third Series, Vol. XVI, No. 96, December 1878). A more recent publication describing the application of phase diagrams in surfactant and emulsion-containing systems is available (see, The importance of mesomorphic (lamellar) phases in emulsion stability, Eccleston, GM, J. Cosmet. Sci. 2001 Mar-Apr;52(2):142; also Spontaneous Emulsification of Oils Containing Hydrocarbon, Nonionic Surfactant, and Oleyl Alcohol, Rang, MJ and Miller, CA, J. Colloid Interface Sci. 1999 Jan 1;209(1):179).

Illustration 1, attached hereto, is a ternary phase diagram for a representative system that exhibits emulsions. The three-component system is that of phosphatidylcholine/oil/water. The oil is a triglyceride (fat), of the type used in typical emulsions, and in fact often in combination with phosphatidylcholine or other lecithin, particularly in pharmaceutical emulsions, such as Diprivan®, and in parentral nutrition, such as Intralipid®. The Examples of Lambert's patent do not use these particular compounds but nevertheless exhibit the same 3-phase equilibrium which dominates the water-rich corner of this phase diagram. Quite broadly, the composition, or "mix point", of an emulsion (typified by the asterisk in this figure) lies in the interior of a 3-phase triangle, as indicated (shaded region), where the three phases are in thermodynamic equilibrium: an aqueous phase, an oil phase containing the active, and a lamellar liquid crystalline phase, fragments of which function to stabilize oil droplets.

In contrast, Illustration 2, attached hereto, shows a phase diagram that is suited for the production of dispersions, as in the instant invention, in which cubic phase particles are dispersed in an aqueous medium. The mix point for such a dispersion is typified by the asterisk-shaped symbol, in the interior of a two-phase region where the cubic phase is in equilibrium with excess water. The equilibria that characterize the instant invention from that of Lambert are strikingly different, as are the particles themselves (substantially liquid oil phase in Lambert, liquid crystalline in the present application), and the location of the active in the oil

droplet, in the case of Lambert, differs from that in the present application (in the liquid crystalline phase).

In view of the above, claims 1, 3-27, and 29-64 should be in immediate condition for allowance.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at the local telephone number listed below to discuss any other changes deemed necessary in a telephonic or personal interview.

A provisional petition is hereby made for any extension of time necessary for the continued pendency during the life of this application. Please charge any fees for such provisional petition and any deficiencies in fees and credit any overpayment of fees to Attorney's Deposit Account No. 50-2041.

Respectfully submitted,

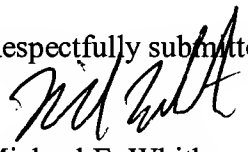

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Illustration 1
Pseudoternary phase diagram
for the system soy phosphatidylcholine / linseed oil triglyceride / water + glycerol.

The phase designations in the illustrations herein are:
L_2 phase, reversed micellar or structureless oil-rich phase;
Q, reversed cubic phase;
$L\alpha$, lamellar phase; and,
H_{II}, reversed hexagonal phase.

The asterisk marks the mix point composition for a typical emulsion, lying in the 3-phase triangle where excess linseed oil, lamellar phase, and water/glycerol are in eulibribium.

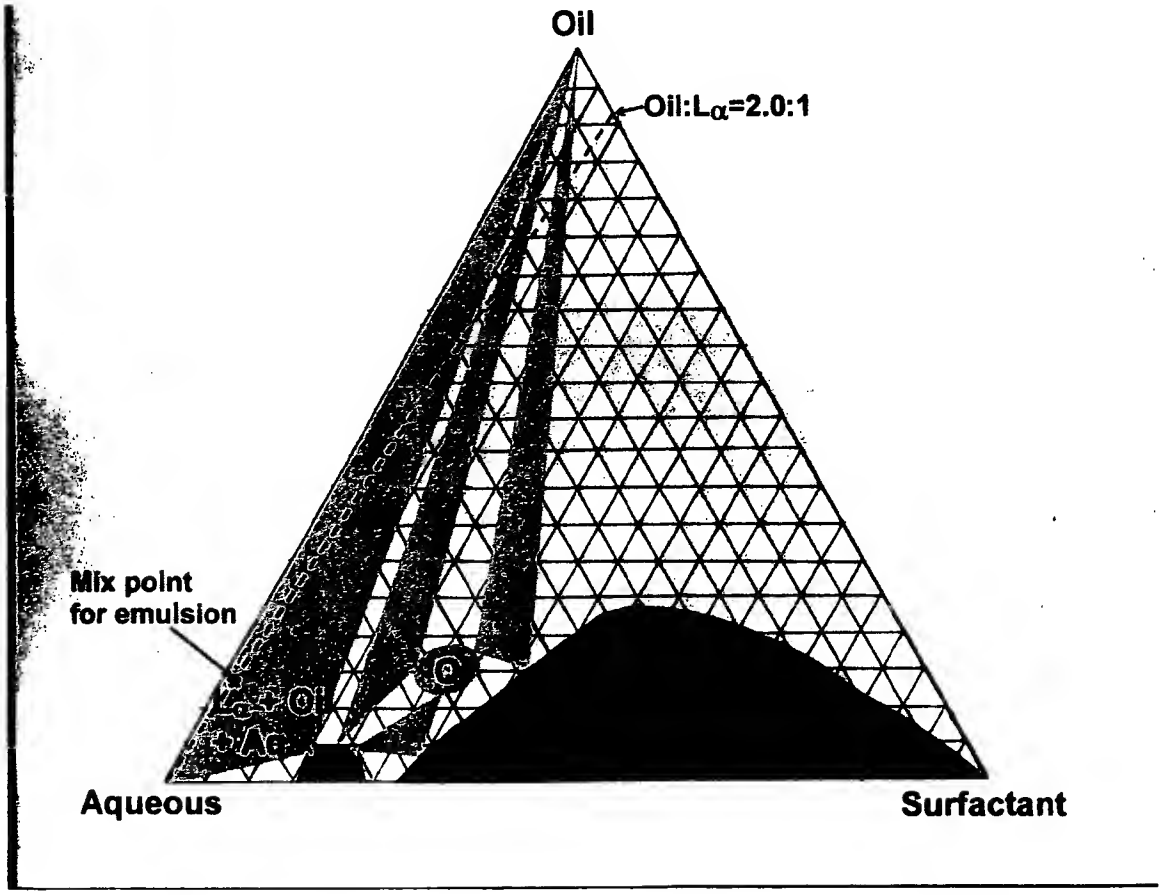

Illustration 2

Pseudoternary phase diagram
for the system phosphatidylcholine + dimyristoylphosphatidylglycerol / water / essential oil of spearmint.

The asterisk shaped symbol shows the composition (mix point) of a typical cubic phase and a typical dispersion of cubic phase particles of the instant invention.